



INSTITUTO SUPERIOR DE CIÊNCIAS DA SAÚDE EGAS MONIZ

MESTRADO INTEGRADO EM MEDICINA DENTÁRIA

FATORES DE RISCO PARA A PERDA DE IMPLANTES E PATOLOGIA PERI-IMPLANTAR NUMA POPULAÇÃO SISTEMICAMENTE COMPROMETIDA

Trabalho submetido por
Joana Leite Neves
para a obtenção do grau de Mestre em Medicina Dentária

setembro de 2015



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Trabalho orientado por
Doutor Pedro Oliveira

e coorientado por
Professor Doutor José Martins dos Santos

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RESUMO

Objetivos: Identificar os possíveis fatores de risco para a perda de implantes e patologia peri-implantar numa população de pacientes sistemicamente comprometidos.

Materiais e métodos: Trata-se de estudo clínico retrospectivo que inclui um total de 721 pacientes sistemicamente comprometidos, submetidos a reabilitações com implantes dentários (422 mulheres, 299 homens) e com idade média de 51 anos (entre 20-87). O tempo médio de seguimento clínico é de 7.3 anos. Foram registadas as variáveis demográficas (idade e género) e as variáveis clínicas (localização dos implantes, tipo de superfície dos implantes e condição sistémica). As variáveis em estudo são a perda de implantes e a patologia peri-implantar. Foram efetuados modelos de regressão logística binários para investigar os efeitos das características demográficas e clínicas dos pacientes para as variáveis dependentes: perda de implantes e patologia peri-implantar. Foi efetuada uma regressão linear para relacionar as características dos pacientes com o número de implantes perdidos. Foram estimados para cada variável o rácio de chances (*odds ratio*) com intervalos de confiança de 95% e níveis de significância correspondentes.

Resultados: A regressão logística multivariada identificou o aumento da idade (pacientes com mais de 40 anos) como fator de risco para a perda de implantes (OR=2.63); e a hepatite como fator de risco para a patologia peri-implantar (OR=3.74). A regressão linear multivariada identificou as doenças reumatológicas e cardiovasculares como estando relacionadas com um número elevado de implantes perdidos.

Conclusão: Tendo em conta as limitações deste estudo, os resultados sugerem que não existem contraindicações absolutas para a reabilitação com implantes numa população de pacientes sistemicamente comprometidos. No entanto, este estudo sugere que o aumento da idade, as condições reumatológicas, as condições cardiovasculares e a hepatite poderão ser tidos em consideração quando se verifica uma influência negativa nos resultados das reabilitações suportadas por implantes.

Palavras-chave: perda de implantes, patologia peri-implantar, implantes dentários, fatores de risco, doenças sistémicas

ABSTRACT

Purpose: The purpose of this study was to identify the possible risk factors for implant failure and peri-implant pathology in a population of systemically compromised patients.

Materials and Methods: This retrospective clinical study included a total of 721 systemically compromised patients (422 women, 299 men), with an average age of 51 years (range: 20-87) rehabilitated with dental implants. The average follow-up time was 7.3 years. The patient's demographic variables (age and gender), and clinical variables (implant location, type of implant surface and systemic conditions) were recorded. Outcome measures were implant failure and peri-implant pathology. Binary logistic regression models were performed to investigate the effect of the patients' demographic and clinical characteristics on the dependent variables implant failure and peri-implant pathology. A linear regression model was performed to correlate the patient's characteristics with the number of failed implants. Odds ratios with 95% confidence intervals and corresponding levels of significance were estimated for each variable.

Results: Multivariate logistic regression disclosed increased age (patients over 40 years of age) as a risk factor for implant failure (OR = 2.63); and hepatitis as a risk factor for peri-implant pathology (OR = 3.74). Multivariate linear regression disclosed rheumatologic and cardiac diseases to be correlated with a higher number of failed implants.

Conclusions: Within the limitations of this study, the results suggest no absolute contraindications for implant rehabilitation in a population of systemically compromised patients. Nevertheless, this study suggests that increasing age, rheumatological condition, cardiovascular condition and hepatitis should be taken into consideration when performing implant supported rehabilitations due to their negative influence on the outcome.

Key Words: implant failure, peri-implant pathology, dental implant, risk factor, systemic disease

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I. Introdução

Os implantes dentários têm vindo a ser utilizados ao longo do tempo como opção de tratamento para a substituição de dentes ausentes. A sua eficácia e previsibilidade está demonstrada através de elevadas taxas de sucesso, revelando-se em geral a melhor opção quando se pretende reabilitar áreas edentulas (Astrand *et al.*,2008; Malo *et al.*,2014; Andersson *et al.*, 2013). Tendo em conta a satisfação por parte dos pacientes, é reportado um aumento do conforto e bem-estar induzido pela melhoria estética e funcional proporcionadas pela reabilitação com implantes, em particular no caso das reabilitações com implantes suportadas por próteses fixas (Annibali *et al.*,2010; Martín-Ares *et al.*,2015).

As reabilitações com implantes tem tido cada vez mais sucesso quer no processo de osteointegração como na satisfação por parte dos pacientes. Contudo, existem um conjunto de fatores que podem levar à perda biológica de implantes, precoce ou tardia. Por sua vez, a perda biológica caracteriza-se pela incapacidade dos tecidos estabelecerem ou manterem a osteointegração, ocorrendo precocemente durante o período de osteointegração ou tardiamente após o mesmo (Esposito *et al.*,1998; Palma-Carrió *et al.*,2011).

Vários autores identificaram um conjunto de potenciais causas para a ocorrência precoce da perda de implantes. Em particular, a condição sistémica, os hábitos tabágicos, a qualidade óssea, o número de implantes colocados e a distribuição dos mesmos (Esposito *et al.*,1998; Palma-Carrió *et al.*,2011; Malo *et al.*,2011; Alsaadi *et al.*,2007). Adicionalmente, Esposito *et al.* (1998) identificou também o trauma cirúrgico associado a um processo de cicatrização debilitado, a contaminação bacteriana e a carga prematura como potenciais causas para a perda precoce de implantes.

Por outro lado, a perda tardia de implantes foi identificada como estando etiologicamente associada ao excesso de carga, à patologia peri-implantar e às características do hospedeiro (Esposito *et al.*,1998; Malo *et al.*,2011; Courts *et al.*,2004; Manor *et al.*,2007; Moy *et al.*, 2005).

Os estudos acima referidos identificam os seguintes fatores endógenos como potenciais fatores de risco para a perda tardia de implantes: idade avançada (Moy *et al.*, 2005;

Manor *et al.*,2007), género masculino (Manor *et al.*,2007), tabagismo e condição sistémica (Esposito *et al.*,1998; Malo *et al.*,2011).

Segundo Manor *et al.* (2007), o excesso de carga foi identificado como o fator proporcionalmente mais relevante para ocorrência de perda de implantes tardia. Decorrendo de um equilíbrio funcional impróprio, em que na presença de patologia peri-implantar poderá promover o aumento desta mesma doença. Esposito *et al.* (1998), salienta que para além do excesso de carga, a persistência de estímulos inflamatórios, provocados por acumulação e maturação de placa bacteriana poderão induzir uma progressiva desintegração da interface implante-osso.

A patologia peri-implantar é classificada como um grupo de situações de origem multifatorial, tais como: a história de periodontite, o nível ósseo localizado no terço médio do implante, a presença de placa bacteriana, hemorragia, o desajuste protético e tipo de material restaurador utilizado. A proximidade com outros implantes ou dentes foi considerado fator de risco para a doença, apenas na presença de placa bacteriana (De Araújo Nobre *et al.*,2015).

Esta patologia está descrita na literatura como “um termo para reações inflamatórias com perda de suporte ósseo que rodeiam um implante em função” (Alberktsson *et al.*, 1994). Na literatura, a patologia peri-implantar é definida clinicamente de diferentes formas (Zitzmann *et al.*,2008). O modo como a incidência da doença é medida também condiciona os resultados. Em particular, varia de 10% a 56% quando o paciente é utilizado como unidade de análise, e de 4% a 43% quando o implante é a unidade de análise (Zitzmann *et al.*, 2008; Froum *et al.*, 2012; Klinge *et al.*,2012; Cecchinato *et al.*, 2014; Atieh *et al.*,2013; Daubert *et al.*, 2015). A falta de consenso relativamente à classificação da patologia peri-implantar e aos seus diferentes graus de severidade, levou a que se propusesse uma classificação segundo o grau de severidade (inicial, moderada ou avançada) tendo em conta “a combinação de hemorragia à sondagem e/ou supuração, profundidade de sondagem e extensão da perda óssea em torno do implante” (Froum *et al.*, 2012). Desta forma, classificou-se a patologia peri-implantar “inicial” mediante a presença de profundidade à sondagem (PS) ≥ 4 mm e com perda óssea $< 25\%$ relativamente ao comprimento do implante. “Moderada”, tendo em conta PS ≥ 6 mm e perda óssea de 25% a 50%. Por último, “avançada” quando se verifica PS ≥ 8 mm e perda óssea superior a 50% (Froum *et al.*, 2012). Consequentemente, esta

classificação permite quer por parte dos clínicos como dos investigadores, uma identificação clara e precisa dos sinais e graus de patologia peri-implantar. Possibilitando assim, um melhor controlo e prevenção da incidência e prevalência da doença, o que aumenta a probabilidade de sucesso e previne a perda de implantes.

Segundo Alsaadi (2008), a localização dos implantes na arcada dentária (maxila ou mandíbula e região anterior ou posterior) tem influência na perda de implantes. Moy (2005) documentou uma maior perda de implantes na maxila relativamente à mandíbula. De Araújo Nobre (2014a) ao estudar a influência de características tais como a localização e posição dos implantes na patologia peri-implantar, verificou que tanto a localização anterior ou posterior, como a localização na arcada (maxila ou mandíbula) não afetam a ocorrência de patologia peri-implantar (Alsaadi *et al.*, 2008; Moy *et al.*, 2005; de Araújo Nobre *et al.*, 2014). Ao avaliar o tipo de superfície dos implantes, Alsaadi (2008) identificou uma tendência para existência de maior perda nos implantes com superfície maquinada relativamente a implantes de superfície tratada através de oxidação anódica (*TiUnite*). Por outro lado, para Renvert (2011), não há evidência de que o tipo de superfície dos implantes possa afetar a ocorrência de patologia peri-implantar (Alsaadi *et al.*, 2008; Renvert *et al.*, 2011)

A perda de implantes e a incidência de patologia peri-implantar, podem ser influenciadas por diversos fatores, em particular a condição sistémica dos pacientes, que se tem vindo a demonstrar como uma área de investigação de grande potencial (Palma-Carrió *et al.*, 2011; Hwang *et al.*, 2007). As condições sistémicas que podem afetar o resultado do tratamento das reabilitações suportadas por implantes são: hepatite, doenças cardiovasculares, doenças da tiroide, diabetes, doenças reumáticas, HIV, doenças oncológicas e hábitos tabágicos (Moy *et al.*, 2005; Coates *et al.*, 2000; Elsubeihi *et al.*, 2002; Hwang *et al.*, 2007; Attard *et al.*, 2002; Ship *et al.*, 2003; Valero *et al.*, 2007; Oates *et al.*, 2009; Weinlander *et al.*, 2010; Krennmair *et al.*, 2010; Balaji *et al.*, 2008; Sham *et al.*, 2003; Baig *et al.*, 2007; Sgolastra *et al.*, 2015).

Os diferentes mecanismos de cada condição sistémica ou de fatores com efeitos nefastos, podem exercer impactos distintos no resultado do tratamento com implantes (Malo *et al.*, 2015).

Um dos fatores de risco amplamente descritos na literatura para a perda de implantes e patologia peri-implantar é o tabagismo. Os efeitos provocados pelos componentes

tóxicos dos cigarros no organismo, induzem a ocorrência de respostas biológicas tais como a redução da cicatrização dos tecidos, provocada pela vasoconstrição e consequente diminuição da perfusão, resultante dos efeitos nefastos do monóxido de carbono e nicotina nas células sanguíneas e nos mecanismos de transporte de oxigénio e celulares (Hwang *et al.*, 2007). Através dos mecanismos anteriormente descritos bem como de um aumento da expressão de mediadores inflamatórios, observa-se nos pacientes fumadores um menor sucesso nos procedimentos cirúrgicos, nas terapias periodontais e tratamento com implantes (Hwang *et al.*, 2007; Balaji *et al.*, 2008; Sham *et al.*, 2003; Baig *et al.*, 2007). Por sua vez, existe um largo consenso no que diz respeito ao impacto negativo do tabagismo nas reabilitações suportadas por implantes (Esposito *et al.*, 1998; Palma-Carrió *et al.*, 2011; Malo *et al.*, 2011; Alsaadi *et al.*, 2007; Moy *et al.*, 2005; Elsubeihi *et al.*, 2002; Hwang *et al.*, 2007; Balaji *et al.*, 2008; Sham *et al.*, 2003; Baig *et al.*, 2007; Sgolastra *et al.*, 2015; Malo *et al.*, 2015; de Araújo Nobre *et al.*, 2014b).

Por outro lado, o impacto de cada doença sistémica nas reabilitações suportadas por implantes, varia de acordo com o seu tipo, sendo sugerido pela literatura que o grau de controlo da doença poderá ser mais importante que a doença *per se* (Diz *et al.*, 2013; Scully *et al.*, 2007).

Assim, são necessários mais estudos que avaliem o impacto das condições sistémicas nas reabilitações suportadas por implantes, de modo a aumentar a probabilidade de sucesso neste tipo de tratamentos.

Este trabalho tem como objetivo principal identificar as possíveis causas para ocorrência de patologia peri-implantar e para a perda de implantes, numa população de pacientes sistemicamente comprometidos ou fumadores.

Os objetivos específicos consistem em identificar (1) a influência de fatores demográficos, como a idade e género para a perda de implantes e patologia peri-implantar; (2) a influência de doenças sistémicas tais como hepatite (A, B e C), doenças cardiovasculares, doenças de tiroide, diabetes, doenças reumatológicas, hábitos tabágicos, HIV+ e doenças oncológicas para a perda de implantes e patologia peri-implantar; (3) a influência da localizações na arcada (maxila ou mandíbula) para a perda de implantes e patologia peri-implantar; (4) e a influência do tipo de superfície do implante (maquinada ou *TiUnit*) na perda de implantes e patologia peri-implantar.

Este estudo abrange uma amostra de 721 indivíduos (com doenças sistémicas ou hábitos tabágicos) reabilitados com 3998 implantes (com uma média 5.5 implantes por paciente) e seguidos longitudinalmente. Em que 422 indivíduos são do género feminino e 299 do género masculino. Apresentam uma média de idade de 51 anos de idade, que varia dos 20 aos 87 anos de idade.

A amostra de pacientes presentes neste estudo permitiu estudar de forma estatisticamente significativa as características desta população, levando à concretização de um artigo científico, submetido na revista “*Journal of Prosthodontics*”.

No futuro é esperado que os resultados deste trabalho possam ajudar a clarificar os fatores de risco para a perda de implantes e para a patologia peri-implantar.

II. Desenvolvimento

Paper: Risk factors for implant failure and peri-implant pathology in a systemic compromised population.

Risk factors for implant failure and peri-implant pathology in a systemic compromised population

Joana Neves, RDH^{1,2}; Miguel de Araújo Nobre RDH, MSc, Epi³; Pedro Oliveira, DDS, MD, PhD¹; José Martins dos Santos, MD, PhD¹; Paulo Maló DDS, PhD⁴

Corresponding author:

Miguel de Araújo Nobre, RDH, MSc Epi

Maló Clinic,

Avenida dos Combatentes, 43, 8 floor, Edifício Green Park,

1600-042 Lisbon, Portugal

Telephone: +351 217 228 100

Fax: +351 217 266 965

e-mail: mnobre@maloclinics.com

¹ Center for Interdisciplinary Research Egas Moniz, Campus Universitário, Quinta da Granja, Monte da Caparica, 2829-511, Caparica, Portugal

² Oral Hygiene Department, Maló Clinic, Avenida dos Combatentes, 43, 9th floor, Edifício Green Park, 1600-042, Lisbon, Portugal.

³ Research and Development Department, Maló Clinic, Avenida dos Combatentes, 43, 8th floor, Edifício Green Park, 1600-042, Lisbon, Portugal

⁴ Department of Oral Surgery, Maló Clinic, Avenida dos Combatentes, 43, 9th floor, Edifício Green Park, 1600-042, Lisbon, Portugal

i. Abstract

Purpose: The purpose of this study was to identify the possible risk factors for implant failure and peri-implant pathology in a population of systemically compromised patients.

Materials and Methods: This retrospective clinical study included a total of 721 systemically compromised patients (422 women, 299 men), with an average age of 51 years (range: 20-87) rehabilitated with dental implants. The average follow-up time was 7.3 years. The patient's demographic variables (age and gender), and clinical variables (implant location, type of implant surface and systemic conditions) were recorded. Outcome measures were implant failure and peri-implant pathology. Binary logistic regression models were performed to investigate the effect of the patients' demographic and clinical characteristics on the dependent variables implant failure and peri-implant pathology. A linear regression model was performed to correlate the patient's characteristics with the number of failed implants. Odds ratios with 95% confidence intervals and corresponding levels of significance were estimated for each variable.

Results: Multivariate logistic regression disclosed increased age (patients over 40 years of age) as a risk factor for implant failure (OR = 2.63); and hepatitis as a risk factor for peri-implant pathology (OR = 3.74). Multivariate linear regression disclosed rheumatologic and cardiac diseases to be correlated with a higher number of failed implants.

Conclusions: Within the limitations of this study, the results suggest no absolute contraindications for implant rehabilitation in a population of systemically compromised patients. Nevertheless, this study suggests that increasing age, rheumatological condition, cardiovascular condition and hepatitis should be taken into consideration when performing implant supported rehabilitations due to their negative influence on the outcome.

Key Words: implant failure, peri-implant pathology, dental implant, risk factor, systemic disease

ii. Introduction

Dental implants are scientifically documented with a high long-term success rate and often represent the best treatment option to replace missing teeth due to their effectiveness and predictability.¹⁻³ Although implant rehabilitations achieve high success rates, there are several situations that can lead to biological implant failure, both early failures (occurring during the osseointegration period) and late failures (after the occurrence of osseointegration).⁴⁻⁵

Previous investigations identified several potential causes for premature implant failure, including smoking habits, systemic condition, bone quality, number of implants placed, and implant distribution.⁴⁻⁷ In addition, factors such as surgical trauma, bacterial contamination and premature loading were previously indicated as potential reasons for early implant failure.⁴ Late implant failures were previously associated with overloading, peri-implant pathology and host characteristics.^{4,6,8-10}

Peri-implant pathology is classified as a group of multifactorial situations,¹¹ being described as “the term for inflammatory reactions with loss of supporting bone tissues surrounding the implant in function”.¹² Peri-implant pathology is clinically defined in different forms by several authors.¹³ Due to those different definitions, the prevalence of the condition is reported in several studies with a wide range, varying between 10% and 56% using the patient as unit of analysis, and between 4% and 43% using the implant as unit of analysis.¹³⁻¹⁸ The lack of consensus on the classification of the different degrees of peri-implant pathology led to the proposal of a classification taking into account the disease severity,¹⁴ classifying the condition as early, moderate or advanced, based on “a combination of bleeding on probing and/ or suppuration, probing depth and extent of radiographic bone loss around the implant”.¹⁴ Consequently, this could enable clinicians and researchers to clearly identify the signs and degrees of peri-implant pathology, in order to prevent/control its incidence/prevalence and therefore maximize the probability of a successful outcome by avoiding implant loss.

Among the possible causes that can influence implant failure and the incidence of peri-implant pathology, the patients' health status is one of the most recently highlighted research line.^{5,21} In particular, systemic conditions/deleterious effect factors such as hepatitis, cardiovascular diseases, thyroid diseases, diabetes, rheumatic diseases, HIV,

oncologic disease, and smoking habits can affect implant supported rehabilitations in their management and/or outcome.^{10, 19-31} The different mechanisms of each systemic condition or deleterious effect factor may exert distinct impact on the implant outcome.³² One of the most reported risk factor for implant failure and peri-implant pathology consists in a deleterious effect factor (smoking habits), with a large consensus on the negative impact on implant supported rehabilitations.^{4-7,10,20,21,28-33} On the other hand, the extent regarding the impact that different systemic disorders might have on the outcome of implant-supported rehabilitations varies according to the type of systemic disorder, with several authors suggesting that the degree of control of the condition could be more important than the condition itself.^{34,35} Therefore, more studies are needed to evaluate the impact of systemic disorders on the outcome of implant-supported rehabilitations in order to increase the probability of the success of such treatments.

The aim of this study was to identify the possible causes of implant failure and peri-implant pathology in a population of patients with systemic conditions or smoking habits.

iii. Materials and Methods

This retrospective clinical study was performed in a private practice (Maló Clinic Lisbon, Portugal). The treatments were performed between May 1995 and August 2012 (last follow-up appointment). This study was approved by an ethical committee (Ethical Committee for Health; authorization 003/2010). This manuscript was written according to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines.³⁶

The sample analyzed was retrieved from a list of patients submitted to implant supported rehabilitations and followed longitudinally: The study included 721 consecutively treated patients (299 males and 422 females), with an average age of 51 years (range: 20-87 years).

Inclusion and Exclusion Criteria

The patients who met the inclusion criteria were identified from the medical records.

Patients were included, provided they were rehabilitated with dental implants for at least one year, and had one or more systemic disease or smoking habits present at the time of implant surgery.

The systemic disorders present in the sample were: hepatitis (A,B, and C), cardiovascular conditions, thyroid conditions, diabetes, rheumatological conditions, smoking habits, HIV+ and oncological conditions. The degree of control for each systemic disorder was not known.

Healthy patients and non-smokers were excluded from the study.

Surgical Protocol

A clinical examination with a preoperative orthopantomography and a computerized tomography scan were used to plan the surgeries. Standard procedures were followed

for the insertion of the implants (Brånemark System® Mk II and Mk III, Mk IV; NobelReplace; and NobelSpeedy; Nobel Biocare AB). Generally, under-preparation was used when a final torque of at least 30Ncm was required before the final seating of the implant. The preparation was performed by full drill depth with a 2.0 or 2.5mm twist drill (depending on bone density), followed by a widening of the cortical bone with a 3-mm twist drill. Countersinking was used only when required to create space for the head of the tilted implants and/or to secure both buccal and lingual cortical bone contact at the implant head in thin bone crests. The implant neck was positioned at bone level, and bicortical anchorage was established whenever possible. After closing and suturing the flap with 3–0 non-resorbable sutures, the access to the abutments was opened by a punch and impression copings were placed.

In case of full-arch rehabilitation (All-on-4 mandible or maxilla), the anterior implants were placed in lateral or central incisor positions and were either 4 or 3.75 mm in diameter, while the posterior implants typically emerging at the second premolar/first molar position were 4 mm in diameter. The posterior implants were inserted just anterior to the foramina and tilted distally about 30 degrees relative to the occlusal plane in the mandible and with 45 degrees of inclination following the anterior sinus wall in the maxilla.

Immediate and Final Prosthetic Protocol

For single teeth or fixed partial prostheses, the intended final abutment was inserted at the time of surgery. The occlusion was adjusted to eliminate direct contact to the prosthesis, and the patients were instructed to avoid biting or chewing directly on the implant-supported crown/bridge. Typically after 6 months, the patients received their permanent prosthetic reconstruction.

For full-arch rehabilitation, based on the impression, a provisional full-arch prostheses of high density acrylic resin (PallaXpress Ultra, Heareus Kulzer GmbH, Hanau, Germany) with acrylic resin crowns (Mondial teeth, Heraeus Kulzer GmbH) and titanium cylinders (Nobel Biocare AB) were manufactured at the dental laboratory and connected on the day of surgery. Final acrylic-resin prostheses of the same type as the provisional prostheses, or metal-ceramic prostheses with a titanium framework and all-

ceramic crowns (Procera forte scanner, Procera and NobelProcera crowns, NobelRondo ceramics; Nobel Biocare AB), were delivered, at the earliest, 6 months post-surgery.

Follow-up

Follow-up clinical examinations were performed for all patients at 10 days, 2, 4, and 6 months after the surgery, and every 6 months thereafter. Data collected in these follow-up appointments were used in this study to evaluate implant failure and peri-implant pathology. The patients' medical records were considered for data collection.

Outcome Measures

Outcome measures were implant failure and peri-implant pathology. Implant failure was defined as the loss of an implant in any patient. Peri-implant pathology was defined as presence of peri-implant pockets >4 mm assessed with a 0.25-Ncm calibrated plastic periodontal probe (Click-probe; Hawe Neos, Bioggio, Switzerland)³⁷ with concurrent presence of bleeding on probing and marginal bone loss with presence or absence of suppuration.

Statistical Analysis

In order to compute the sample of this study, data was summarized in frequencies for patient's baseline characteristics taken in consideration in this study. Frequencies summarized per patient were the number of implants placed, the number of failed implants, and the number of implants with peri-implant pathology. The patient's baseline characteristics taken into account were gender, age and systemic condition. The variable "age" was divided in three categories (less than 40 years, 40 to 59 years, and older than 59 years).

Multivariable binary logistic regression and linear regressions were performed to evaluate the relationships between the patient's characteristics and the occurrence of implant failure, the occurrence of peri-implant pathology, and the number of implant failures per patient.

To identify the factors affecting implant failure, peri-implant pathology, and the number of failed implants per patient, the independent variables included in the models were age, gender and coexisting conditions (hepatitis, cardiovascular condition, thyroid condition, diabetes, rheumatologic condition, HIV+ and smoking habits).

Odds ratios (OR) with 95% confidence intervals and corresponding p-values were estimated for each independent variable when controlled for the presence of the other variables of interest. The level of significance conserved was 5%. Statistical analysis was performed using the software STATA version 13 (StataCorp LP, College Station, Texas, USA).

iv. Results

Patient characteristics

The systemic disorders included patients with: hepatitis (n=15 patients); cardiovascular diseases (n=222 patients); thyroid diseases (n=37 patients); diabetes (n=56 patients); rheumatic diseases (n=36 patients); smokers (n=476 patients); HIV (n=5 patients); oncological condition (n=7 patients).

Dental implants and implant failure

From the 721 patients included in the study, 97 presented at least an implant failure, rendering an implant failure rate of 13.5%. A total of 3998 implants were considered in this study (average of 5.5 implants per patient) with a global failure rate of 4.3% (n=173 implant failures). From the 3998 implants used in the study, 2262 were placed at the maxilla with a failure rate of 5.3% (n=119 implant failures) and the 1736 implants placed at the mandible had a loss rate of 3.1% (n=54 implant failures). Regarding the type of implant surface, there were 820 implants with machined surface and 3178 implants with anodically oxidized surface, with a failure rate of 10.9% (n=89 implant failures) and 2.6% (n=84 implant failures), respectively.

Patients over 40 years old were a predictor for implant failure when controlled for the presence of the other variables of interest, with more than two times the odds of implant failure (OR= 2.6) and two times the percentage of implant failures (14.7%) when compared to the reference category (patients under 40 years old; Table 1). Implant failure was not dependent from gender, nevertheless the higher failure rate occurred in male patients (15.4% vs. 12.7% of female patients). The coexisting conditions HIV+, hepatitis, rheumatologic condition and smoking habits registered higher failure rates with 40.0%, 16.7%, 19.4% and 14.9%, respectively. Diabetes was the systemic condition with lower implant failure rate (7.1%). The coexisting systemic conditions did not affect implant failure significantly. Nevertheless, it was registered that rheumatologic disorder affected implant failure at the 10 per cent level of significance (OR = 2.51, P<0.1).

Variable	No. of Patients	Failure (%)	Success (%)	OR	P value	95% CI	
<i>Age</i>							
< 40	123	7.3	92.7	1.00		Reference	
40-59	440	15.5	84.6	2.64	0.01*	1.26	5.54
> 59	158	12.7	87.3	2.63	0.03*	1.07	6.46
<i>Gender</i>							
Female	422	12.1	87.9	1.00		Reference	
Male	299	15.4	84.6	1.38	0.16	0.88	2.17
<i>Coexisting Conditions</i>							
Hepatitis	12	16.7	83.3	0.99	0.99	0.19	5.08
Cardiac disease	222	10.8	89.2	0.92	0.82	0.46	1.84
Thyroid	37	13.5	86.5	1.45	0.50	0.49	4.31
Diabetes	56	7.14	92.9	0.48	0.17	0.16	1.38
Rheumatologic disease	36	19.4	80.6	2.51	0.06	0.94	6.69
Smokers	476	14.9	85.1	1.77	0.14	0.84	3.75
HIV+	5	40.0	60.0	3.74	0.17	0.56	24.85

OR= Odds Ratio **Significant at $P < .05$; *Significant at $P < .01$

Table 1 Binary logistic regression model for the effect of the independent variables on implant failure.

Results obtained from the multiple linear regression (Table 2) yielded rheumatologic and cardiovascular disorders, as well as the number of implants placed per patient as significant predictors ($P < 0.01$) for the number of implants lost.

Peri-implant pathology

A total of 244 patients (33.8%) and 506 implants (12.7%) registered peri-implant pathology. The peri-implant pathology rate according to implant position was 10.1% ($n=176$) in the mandible and 14.6% ($n=330$) in the maxillae. According to the type of implant surface, peri-implant pathology was registered in 13.2% ($n=108$) and 12.5% ($n=398$) of the machined surface and anodically oxidized surface implants, respectively.

Regarding the possible risk factors for peri-implant pathology in the present population, the variables smoking habits, hepatitis and HIV+ registered a higher risk of developing peri-implant pathology (36.6%, 66.7%, and 60.0%, respectively), while thyroid disorders registered a lower risk of developing peri-implant pathology (18.9%).

Based on the logistic regression model, hepatitis was the only risk factor for peri-implant pathology (OR= 3.74, $p<0.05$) when controlled for the presence of the other variables of interest (Table 3).

Variable	Coefficient	(Std. Err.)
No. of placed implants	0.093*	(0.035)
<i>Age</i>		
< 40	Ref. Cat.	
40-59	-0.200	(0.442)
> 59	-0.078	(0.556)
<i>Gender</i>		
Female	Ref. Cat.	
Male	-0.404	(0.258)
<i>Coexisting Conditions</i>		
Hepatitis	-0.323	(0.967)
Cardiac disease	1.125**	(0.401)
Thyroid	-0.273	(0.620)
Diabetes	-0.965	(0.619)
Rheumatologic disease	2.203**	(0.550)
Smokers	0.776	(0.452)
HIV+	-0.445	(0.978)
Sample Size	97	
R^2	0.369	
$F_{(11,85)}$	4.51	

Table 2 Number of failed implants as a function of patient characteristics using multivariable linear regression.

Variable	No. of Patients	Failure (%)	Success (%)	OR	P value	95% CI	
<i>Age</i>							
< 40	123	31.7	68.3	1.00		Ref. Cat.	
40-59	440	35.2	64.8	1.29	0.26	0.83	2.01
> 59	158	31.7	68.4	1.25	0.44	0.71	2.23
<i>Gender</i>							
Female	422	33.2	66.8	1.00		Ref. Cat.	
Male	299	34.8	65.2	0.98	0.92	0.71	1.36
<i>Coexisting Conditions</i>							
Hepatitis	12	66.7	33.3	3.74	0.04*	1.09	12.84
Cardiac disease	222	32.0	68.0	1.14	0.61	0.69	1.88
Thyroid	37	18.9	81.1	0.57	0.23	0.23	1.41
Diabetes	56	26.8	73.2	0.76	0.41	0.41	1.44
Rheumatologic disease	36	25.0	75.0	0.75	0.51	0.32	1.75
Smokers	476	36.6	63.5	1.48	0.15	0.87	2.53
HIV+	5	60.0	40.0	2.34	0.37	0.36	15.19

OR= Odds Ratio **Significant at P <.05; *Significant at P<.01

Table 3 Binary logistic regression model for the effect of the independent variables on peri-implant pathology

v. Discussion

In this study, the authors proposed three models with risk factors for implant failure, higher number of failed implants and peri-implant pathology, in patients systemically compromised. The results suggest the impact of some systemic health factors and demographic factors on implant failure and peri-implant pathology.

Regarding the factors associated with implant failure, the demographic variable “age” revealed a significant association, judging by the higher odds for implant failure in patients over 40 years with patients between 40-59 years and patients with more than 60 years, exhibiting more than 2 times the odds for implant failure when compared to patients with less than 40 years of age. This result registered in our study using a large sample of systemically compromised patients was outlined in previous research using smaller samples:^{9,10} Moy et al.¹⁰ in a retrospective cohort study analyzed dental implant failure rates and associated risk factors, and observed that increasing age was strongly associated with the risk of dental implant failure, with patients between 60-79 years registering a higher relative risk for implant failure (RR=2.24). Another retrospective cohort study by Manor et al.⁹ to evaluate the characteristics of early and late implant failure conducted in 194 patients who presented implant failures during a 6-year period, reported old age as one of the factors for late dental implant failure.

Concerning the sub-sample of patients with implant failure, the factors associated with a higher number of implant failures were the presence of rheumatologic or cardiovascular conditions. Furthermore, in the linear regression model, rheumatologic conditions had a risk of failed implants that was twice the risk for cardiovascular conditions. Rheumatic conditions include more than 150 diseases and syndromes. They are categorized from different types of disorders, with some of those disorders revealing a great impact on society, such as: rheumatoid arthritis, osteoarthritis and osteoporosis.⁴⁰ Different rheumatic conditions can influence implant success in different ways:^{26,27,34} Several authors indicate a small effect of rheumatic diseases on implant failure, namely in osteoporosis and rheumatoid arthritis.^{20,21,26,27,34,41,42} However, previous studies registered a negative influence of rheumatic conditions such as connective tissue diseases, the taking of bisphosphonates and osteoporosis on implant survival rates.^{7,26,27,39} Krennmairet et al.²⁷ observed that

patients with rheumatoid arthritis and connective tissue diseases had increased bone resorption and more vulnerable soft-tissue conditions than patients with isolated rheumatoid arthritis ($p < 0.01$). Weinlander et al.²⁶ in a retrospective study identified patients with connective tissue diseases present an increased bone resorption (mean: 3.1 mm \pm 0.7 mm) and more peri-implant soft tissue alterations (bleeding index) than patients suffering from rheumatoid arthritis. Moreover, Zahid et al.³⁹ in a retrospective study concluded that patients taking bisphosphonates could be at higher risk for implant thread exposure (OR= 3.25). Furthermore, Alsaadi et al.⁷ in a retrospective study identified osteoporosis as a significant factor for implant failure on a multivariate logistic regression (OR=2.88). The analysis of the literature and the results of our study suggest at least caution when managing dental implant rehabilitation in these patients.

On the other hand, cardiovascular diseases are a group of disorders that include hypertension, atherosclerosis, vascular stenosis, coronary artery disease, and congestive heart failure. The mechanism of osseointegration and healing process compromising situations can be described by a compromised blood flow which may restrict oxygen supply and nutrients to the tissues.^{20,21} Nevertheless, several studies registered no evidence that controlled cardiovascular diseases increased the risk of implant failure.^{7,20,21,34} These potential contradictory results may be explained by the degree of systemic disease control. In fact, this factor has been previously proposed to be of higher significance than the systemic condition itself.^{34,35} However, the degree of systemic disease control was not known in our study and therefore this question remains open.

Concerning peri-implant pathology, the only risk factor registered in this study was the presence of hepatitis. Despite the low number of studies in the literature, a previous report registered a significant alteration in salivary flow in a group of patients with hepatitis C, which had a significant impact on oral disease, namely the increase of decays, gingival bleeding and deep pockets.¹⁹ Marrone et al.³⁸ in a cross-sectional study, evaluated the possible risk indicators for peri-implant pathology assessing implant and patient characteristics, registering a stronger association between hepatitis and peri-implant pathology (OR=2.9).

Despite the non-significant effect of smoking habits on implant failure and peri-implant pathology registered in our study, a large number of the studies in the literature

report the strong influence of smoking habits on the implant failure and peri-implant pathology,^{5,7,20,21,28-33,43} affecting the oral tissues' healing process, periodontal procedures and implants therapies.^{21,28-30} Nevertheless, Alssadi et al.⁴² in a retrospective study reported that smoking did not seem to be relevant player in the etiology of late implant loss; while Renvert et al.⁴⁴ in a systematic review, suggested smoking should be accounted for as a confounding variable in the etiology of peri-implant infections. Our study accounted with the presence of that possible confounding effect of smoking, by including it in the logistic regression analysis, a statistical procedure that could explain the non-significant result.

The limitations of this study include a single center, the retrospective analysis and the lack of a healthy patients' control group, which can influence the external validity of the study and the extrapolation to other population. A further limitation is the lack of analysis of potential risk factors described in the literature such as "history of periodontitis",^{33, 43-44} the level of oral hygiene,^{33, 43-44} and the degree of systemic disease control which could have provided sub-group analysis within this population of systemic compromised patients.

Future studies should investigate the influence of the degree of systemic disease control on the long-term outcome of implant supported rehabilitations in systemically compromised patients, using prospective study designs with healthy control groups, while controlling for the presence of other potential risk factors.

vi. Conclusions

Based on the results of our study, it is concluded that increasing age in patients systemically compromised is associated with higher risk of implant failure; rheumatologic and cardiovascular disorders were associated with a higher number of implant failures; and that hepatitis was associated with a higher risk of peri-implant pathology, suggesting caution in the management of these patients for implant rehabilitation. Nevertheless, this study did not identify any absolute contraindications to dental implant rehabilitation judging by the absolute implant failure rate, suggesting a favorable risk/benefit ratio for the rehabilitation of these patients.

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III. Conclusões

Tendo em conta os resultados estatísticos, o estudo sugere o impacto das seguintes condições sistémicas e fatores demográficos na perda de implantes:

1. Aumento da idade, em que pacientes dos 40-59 anos e acima dos 60 anos de idade, apresentam o dobro da probabilidade para a perda de implantes quando comparados com pacientes abaixo dos 40 anos de idade.
2. A presença de doenças reumatológicas e doenças cardíacas estão associadas a um aumento do número de implantes perdidos ao estudar o grupo de pacientes que perderam implantes. No entanto verifica-se o dobro dos implantes perdidos nos pacientes com doenças reumatológicas.

Relativamente à ocorrência de patologia peri-implantar, o estudo indica:

3. Uma maior incidência da doença em pacientes com hepatite (A, B ou C).

Os resultados obtidos sugerem que se tenham algumas precauções ao reabilitar com implantes o grupo de pacientes acima descritos. Por sua vez, o estudo não identifica qualquer tipo de contraindicações absolutas para a reabilitação com implantes, uma vez que a taxa de perda de implantes absoluta sugere um risco/benefício favorável para os pacientes nestas condições.

As limitações inerentes a este estudo compreendem: (1) o facto de incluir apenas um único centro dentário; (2) o facto de ser um estudo retrospectivo sem um grupo controlo de pacientes saudáveis, que por sua vez poderá influenciar a validade externa do estudo bem como a sua extrapolação para a outra população; (3) a ausência do estudo de potenciais fatores de risco descritos na literatura tais como a “história de periodontite” e “o nível de higiene oral” (De Araújo Nobre *et al.*, 2014b; Mombelli *et al.*, 2012; Renvert *et al.*, 2009); (4) o desconhecimento sobre o grau de controlo de determinadas doenças sistémicas presentes na população; (5) o desconhecimento sobre qual o subtipo de determinados grupos de doenças sistémicas presentes no estudo.

Em investigações futuras, ao estudar os resultados a longo-termo de pacientes sistemicamente comprometidos que foram reabilitados com implantes é importante que se tenha em conta o grau de controlo de cada doença. Assim como a identificação do subtipo de doença de cada grupo. É importante que se utilizem estudos prospetivos, grupos controlo de pacientes saudáveis e que se controle a presença de outros potenciais fatores de risco, tais como a “história de periodontite”, “nível de higiene oral” ou a “existência de problemas mecânicos”, uma vez que tanto a perda de implantes como a patologia peri-implantar decorrem de causas multifatoriais (Manor *et al.*, 2007; De Araújo Nobre *et al.* 2014c).

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ANEXOS



**Risk Factors for Implant Failure and Peri-implant pathology
in a systemic compromised population**

Journal:	<i>Journal of Prosthodontics</i>
Manuscript ID	Draft
Wiley - Manuscript type:	Original Manuscript
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